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# Regional Brain Activity in Chronic Schizophrenic Patients during the Performance of a Verbal Fluency Task

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**Background.** This study examined the pattern of cerebral blood flow observed in chronic schizophrenic patients while they performed a paced verbal fluency task. Such tasks engage a distributed brain system associated with willed action. Since willed action is impaired in many chronic schizophrenic patients we hypothesised that task performance would be associated with an abnormal pattern of blood flow.

**Method.** Positron emission tomography (PET) was applied to 18 chronic schizophrenic patients stratified into three groups on the basis of verbal fluency performance and current symptoms. Regional cerebral blood flow (rCBF) was measured while the patients performed (a) verbal fluency, (b) word categorisation, and (c) word repetition. Results were compared with six normal controls matched for age, sex and premorbid IQ. Analysis was restricted to six brain regions previously identified in studies of normal volunteers.

**Results.** In five brain areas, including the left dorsolateral prefrontal cortex, the patients showed the same pattern of activation as control subjects. However, in the left superior temporal cortex, all patient groups failed to show the normal decrease in blood flow when verbal fluency was compared with word repetition.

**Conclusion.** These observations suggest that (a) chronic schizophrenic patients can show a normal magnitude of frontal activation when matched for performance with controls, and (b) they fail to show the expected reductions of activity in the superior temporal cortex. This latter result may reflect abnormal functional connectivity between frontal and temporal cortex.

Since the classic study of Ingvar & Franzen (1974), there have been many investigations of schizophrenia by functional brain imaging (Andreasen *et al*, 1992). Most (~60%) have observed a relative reduction in frontal metabolism in patients scanned at rest (hypofrontality). However, many studies (~40%) found no evidence of hypofrontality and a few observed hyperfrontality. There are good reasons why resting scans of schizophrenic patients should lead to contradictory results. Mental activity is associated with detectable brain activity even when no overt behaviour occurs (e.g. Stephan *et al*, 1995). Schizophrenic patients vary widely in their current mental state, and thus varying patterns of cerebral blood flow are to be expected in unselected groups. Liddle *et al* (1992) confirmed that current symptoms are related to regional cerebral blood flow (rCBF). Hypofrontality (particularly in the left dorsolateral prefrontal cortex (DLPFC)) was found to be associated with psychomotor poverty (poverty of speech, flattening of affect, and motor retardation). However, even though schizophrenic symptoms segregate into clusters, and different patterns of resting cerebral blood flow can be associated with these syndromes, it remains likely that a core abnormality is present in all schizophrenic patients.

An important approach to the problem of the variability in mental states during brain imaging is to control mental state, at the time of scanning, by applying a psychological challenge. This involves presenting a task during the scan which elicits specific mental processes. This method can not only reduce variability between subjects, but also highlight brain areas of interest. For this purpose, various studies have used psychological tasks sensitive to frontal lobe damage. When normal volunteers perform such tasks, there is an associated increase in frontal blood flow. However, in schizophrenic patients, who perform such tasks poorly, this increase is often reduced or absent (Weinberger, 1986). This observation is particularly marked in patients with negative features (Andreasen *et al*, 1992). At the cognitive level of description, the behaviour of such patients reflects a specific problem with self-generated or 'willed' acts (Frith, 1992, chapter 4). We have identified an extended system of brain areas,

1. This was the last study completed by Sigrid Herold before her untimely death in 1992.

including the DLPFC, which are activated during such acts (Frith *et al*, 1991*a*,*b*; Friston *et al*, 1993). One of the tasks used in these studies is a paced form of verbal fluency (another task sensitive to frontal lobe damage), which is particularly suitable for use with patients. We have used this task, along with appropriate control tasks, to study the pattern of blood flow associated with willed actions in chronic schizophrenic patients.

## Method

### Subjects

Eighteen chronic schizophrenic in-patients were recruited from various West London hospitals. These patients are very similar to those studied by Liddle *et al* (1992). They were selected for reasonably stable symptoms which were reassessed (by SH) shortly before the scan was done. At the same time that this detailed examination of mental state was done, the patients also completed a series of verbal fluency tests and were assessed for premorbid IQ (Nelson & O'Connell, 1978). The patients were divided into three groups on the basis of their verbal fluency performance assessed before scanning. Membership of group 1 (poor verbal fluency) implied less than 24 items on the standard FAS test (number of words beginning with the letters *F*, *A*, and *S* in one minute each). Membership of group 2 (odd verbal fluency) implied production of neologisms or more than five out-of-category/unusual items. Unusual items in the categories of animals and fruit were identified on the basis of the Battig & Montague (1969) category norms. Membership of group 3 (normal verbal fluency) implied that more than 24 items were produced on the FAS test with fewer than five odd items. Table 1 lists the background characteristics of these three groups, while Table 2 lists their clinical features. All but one patient had marked negative signs, as would be expected in this severe and chronic group. However, those with poor verbal fluency showed a much higher severity of negative features. The disorganised patients tended to be in the group who gave odd semantic responses, while patients with hallucinations and delusions tended to be in the group with normal verbal fluency.

In addition, we recruited six normal volunteers who were matched for age, sex and premorbid IQ with the schizophrenic patients (Table 1). Although their premorbid IQ was in the normal range, many of the patients showed the low level of intellectual function characteristic of chronic schizophrenia.

### Activation tasks

The brain images obtained with positron emission tomography (PET) are essentially integrative since all the activity occurring during the period of the scan is added together. In consequence, the result is very sensitive to the rate at which stimuli are presented (Price *et al*, 1992) or responses are made (Jenkins, personal communication). We therefore used paced tasks to ensure, as far as possible, that all subjects received the same number of stimuli and made the same number of responses during the scan.

The principal experiment task (fluency) was a paced form of orthographic verbal fluency. Every five seconds the experimenter named a letter, and the subject responded by giving a word beginning with that letter (e.g. *A – apple*). The same letter was repeated 10 times in succession unless the subject was unable to produce any more examples, in which case a new letter was used. The rate used was slow enough for all the patients to respond. Although patients and controls were giving the same number of responses during the scan, this does not mean that they were

Table 1
Background variables in four groups: means (SDs)

| | Controls | Schizophrenics (verbal fluency performance) | | |
|---|---|---|---|---|
| | | Normal | Odd | Poor |
| *n* (male:female) | 6 (5:1) | 6 (5:1) | 4 (4:1) | 7 (5:2) |
| Age (years) | 57.2 (6.7) | 47.7 (6.5) | 53.0 (11.5) | 57.9 (10.5) |
| NART | 109 (7.2) | 102 (14.6) | 109 (8.4) | 99.3 (8.6) |
| FAS | 37.5 (11.9) | 33.3 (4.7) | 33.4 (11.1) | 18.9 (2.6) |
| Odd items | 1.5 (1.1) | 3.3 (1.6) | 17.2 (15.0) | 2.7 (1.4) |

NART: National Adult Reading Test (Nelson & O'Connell, 1978).
FAS: number of words generated in 1 minute beginning with *F*, *A*, and *S*.
Odd items: from semantic fluency test; animals, fruit.
All assessments were made a few days before scanning.

Table 2
Clinical variables in schizophrenic patients

| | Schizophrenic patients (verbal fluency performance) | | |
|---|---|---|---|
| | Normal | Odd | Poor |
| Length of illness, years: mean (SD) | 20.5 (12.2) | 22.4 (14.3) | 27.3 (16.3) |
| Poverty: incidence | 100% | 80% | 100% |
| Mean severity (SD) | 3.5 (1.1) | 4.0 (3.2) | 8.7 (2.0) |
| Disorganisation: incidence | 33% | 80% | 43% |
| Reality distortion: incidence | 100% | 60% | 29% |

Poverty: poverty of speech, flattening of affect, retardation.
Disorganisation: incoherence of speech, incongruity of affect.
Reality distortion: delusions, hallucinations.

performing the task equally well. Although we did not measure this formally, it could be observed that many patients took longer to produce a response than the controls. We have previously shown that unpaced (Frith *et al*, 1991*a*) and paced (Frith *et al*, 1991*b*) versions of verbal fluency are associated with essentially the same pattern of brain activity.

In the second task (classification), the experimenter read out a series of nouns, and the subject responded by classifying them as man-made or natural (e.g. *spoon*: man-made, *robin*: natural). The rate was the same as in the first task. This task involves semantic analysis, but the response is determined by the stimuli, so that there is no need for a self-generated response.

In the third task (repetition), the experimenter read out a series of nouns and the subjects simply repeated what they heard. The rate of presentation was the same as in the previous two tasks. In this task, input (hearing a word) and output (saying a word) are the same as in the other two tasks. However, the response is completely specified by the stimulus, and so processing is minimised.

Each task was performed twice in a balanced order that was the same for all subjects (1 2 3 3 2 1) to minimise order effects.

One patient in the group with poor verbal fluency was unable to perform the categorisation task. However, complete data were available for the generation and repetition conditions. An average of 33 words was produced during each scan. This is equivalent to a rate of ~8 words per minute and was within the capacity of all the patients. The variation in the number of words produced was within 10%, and there were no significant differences between the groups or the conditions.

### Scanning procedure

rCBF was measured by recording the distribution of cerebral radioactivity while subjects inhaled $C^{15}O_2$ at a concentration of 6 mBq/ml and a flow rate of 500 ml/min through a standard oxygen mask for a period of 2 min with the CTI 931-08/12 PET scanner (CTI, Inc, Knoxville, TN, USA). Each rCBF scan was divided into three frames: a) a 30-s measurement of background radiation; b) 2-min rCBF measurement during inhalation of tracer; c) a 90-s wash-out. After correction for background radioactivity, scans were corrected for attenuation (measured by a transmission scan), and the scans were reconstructed in 15 axial planes by three-dimensional filtered back projection with a Hanning filter with a cut-off frequency of 0.5 cycles pixel$^{-1}$. The resolution of the resulting images was $8.5 \times 8.5 \times 8.0$ mm at full-width half-maximum (FWHM). The integrated counts over the second PET frame were used as rCBF equivalents.

### Image analysis

Image analysis was done on a SPARC II workstation (SUN Microsystems Europe, Inc, Surrey, UK) with ANALYZE (BRU, Mayo Foundation, Rochester, MN, USA) and PRO MATLAB (Mathworks Inc, Natick, MA, USA). The 15 original scan slices (6.75 mm interplane distance) were interpolated to 43 planes in order to render the voxels approximately cubic. The six images from each subject were transformed into a standard stereotactic space corresponding to the atlas of Talairach & Tournoux (1988), the intercommissural line being used as the reference plane for the transformation. In this space, one pixel represents 2 mm in the $x$ and $y$ dimensions with an interplanar distance of 4 mm, allowing direct cross reference to the topography of the stereotactic atlas. Each image was smoothed with a 10-pixel-wide Gaussian filter to increase the signal-to-noise ratio and accommodate normal variability in functional and gyral anatomy.

### Statistical analysis

Since data were available for a relatively small number of subjects, we chose to examine only six brain areas. These had been identified in previous studies by the same activation tasks (fluency and repetition), and they form an extended network concerned with self-generated verbal responses. The brain areas and their coordinates in Talairach space are listed in Table 3. Five areas are taken from Frith *et al* (1991*b*). The sixth area, the thalamus, was not seen in that study, but did appear in a later study (Frith *et al*, 1993), which used a more sensitive method.

Blood-flow values were extracted for each subject at each of these six coordinates, corrected for differences in global flow between conditions. Given the smoothing that had been applied, this was equivalent to taking the average blood flow in a 10 mm sphere of tissue centred on the coordinates specified.

Table 3
Brain areas defined from previous studies

| Brain area | Talairach coordinates (mm) | | |
|---|---|---|---|
| | *x* | *y* | *z* |
| Left dorsolateral prefrontal cortex[1] | −42 | 30 | 20 |
| Anterior cingulate cortex[1] | 4 | 24 | 36 |
| Posterior cingulate cortex[1] | 0 | −50 | 24 |
| Left superior temporal gyrus[1] | −46 | −22 | 4 |
| Right superior temporal gyrus[1] | 44 | −14 | 12 |
| Thalamus[2] | −4 | −16 | 4 |

[1]Frith *et al* (1991*b*); [2] Friston *et al* (1993).

A repeated-measures ANOVA was then done for each region. There were two within-subject factors (conditions and replications). First, the schizophrenic subjects as a whole were compared with the controls, and then the three schizophrenic groups were compared.

## Results

In five of the six regions, there were highly significant differences between the conditions just as had been seen in the previous studies (Table 4). These differences were observed in the normal control group and in the schizophrenic patients. In the fluency condition relative to the repetition condition, there were increases in the left DLPFC, in the anterior cingulate cortex, and in the thalamus. There were decreases in the posterior cingulate cortex and the right superior temporal gyrus. There were no interactions with diagnosis in any of these areas, confirming that the schizophrenic patients showed the same pattern of activity as the controls. In every region, the activity associated with the categorising task fell between that in the generating and the repetition tasks (Table 5).

In only one area, the left superior temporal gyrus, did the interaction between conditions and groups reach significance ($F(2, 44) = 4.61$, $P < 0.02$). In the control group, there was a significant difference between conditions in this area ($F(2, 10) = 6.12$, $P < 0.03$), such that more activity was observed during repetition than during generation. There was no significant difference between conditions in the schizophrenic group ($F(2, 34) = 0.95$).

Table 4
Two-way ANOVA (groups times conditions) on the six regions of interest. Controls (6) *v.* schizophrenic patients (18) (d.f. = 2, 44)

| Area | Conditions | Effect | Interaction with group | |
|---|---|---|---|---|
| | F value | *P* value | F value | *P* value |
| DLPFC | 8.24 | 0.002 | <1 | NS |
| Anterior cingulate cortex | 6.56 | 0.02 | 1.9 | NS |
| Posterior cingulate cortex | 11.51 | 0.002 | <1 | NS |
| Thalamus | 10.19 | 0.002 | <1 | NS |
| Left superior temporal gyrus | 1.64 | NS | 4.61 | 0.02 |
| Right superior temporal gyrus | 7.06 | 0.02 | <1 | NS |

Details of the interaction in left temporal area

| | Conditions | Effect |
|---|---|---|
| | F value | *P* value |
| Controls | 6.12 | 0.03 |
| Schizophrenic patients | 0.95 | NS |

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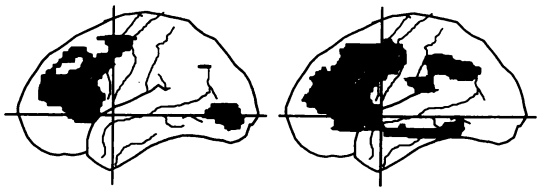
Table 5
Mean values for three conditions in six regions of interest (rCBF adjusted ml/dl per min). Data for first five regions combines schizophrenic patients and controls

| | Generate | Categorise | Repeat |
|---|---|---|---|
| Dorsolateral prefrontal cortex | 47.23 | 46.66 | 45.81 |
| Anterior cingulate cortex | 61.40 | 60.88 | 60.45 |
| Posterior cingulate cortex | 60.06 | 60.55 | 61.14 |
| Thalamus | 65.76 | 64.61 | 64.22 |
| Right superior temporal gyrus | 64.58 | 64.81 | 65.42 |
| Left superior temporal gyrus | | | |
| Controls | 65.87 | 66.86 | 67.25 |
| Schizophrenic patients | 66.91 | 66.45 | 66.67 |

No significant differences between the subgroups of schizophrenic patients were found in any of the six areas. Figure 1A shows the pattern of activation associated with generation (generation–repetition) in the control subjects, while Figure 1B shows the pattern of activation in the patients with poor verbal fluency. For both groups, there was clear evidence of activation of the left DLPFC. Inspection of the figures suggests that the area of activation was, if anything, larger in the schizophrenic group, but at present we do not have a method for quantifying this impression. A much less conservative analysis (statistical parametric mapping (SPM)) confirmed the findings revealed by the ANOVA reported above. The SPM analysis also revealed some additional areas where the groups differed. Since these areas had not been observed in our previous studies of verbal fluency, further experimentation is needed before these results can be fully interpreted.

## Discussion

There are two major findings in this study of brain activation in chronic schizophrenic patients. First, when these patients were performing a paced word-generation task, they showed activation in the left DLPFC in the same location as that previously observed in young normal volunteers. Furthermore the magnitude of the activation (as compared with word-repetition task) did not differ from that observed in normal controls matched for age, sex and premorbid IQ. This result appears to be very different from those observed in previous studies. Several studies, including one of our own, have reported reduced blood flow in the DLPFC in schizophrenic patients during resting scans. This phenomenon seems to be associated with negative symptoms such as poverty of speech (Liddle *et al*, 1992), and we presume that it reflects a lack of spontaneous mental activity in these patients. Of course, there is no reason why low *resting* flow in the DLPFC should relate to lack of *activation* when a task is performed. Indeed, with a lower starting-point, there might be more capacity for increases in activity.



(A) (B)

Fig. 1 Lateral views of left hemisphere of brain derived from the atlas of Talairach and Tournoux (1988). Horizontal and vertical lines define *y* and *z* axes of stereotactic space with its origin in anterior commisure. Areas of significantly increased blood flow occurring during word-generation tasks have been superimposed. A) Left image: data from six normal controls. B) Right image: data from six schizophrenic patients with poor verbal fluency and negative signs. Activation of left dorsolateral prefrontal cortex can be seen in both images.

However, several reports have also shown that chronic schizophrenic patients fail to activate frontal cortex when performing 'frontal' tasks. This is most striking in the series of studies reported by Weinberger *et al* (1986) with the Wisconsin Card Sorting test. One difficulty with the interpretation of these and similar studies is that the patients were worse at performing the task than the controls. If 'worse' performance was associated with reduced rate of occurrence of certain critical processes, this could account for differences in the magnitude of activation observed in the scan. We avoided this problem by using a paced task. However, slowness is not the only possible reason for poor performance. Tasks as complex as the Wisconsin Card Sorting test can be performed in many different ways. Some strategies may involve processes which do not engage the DLPFC. Raichle *et al* (1994) have shown that normal volunteers can perform a verb-generation task using two different neural systems. When the

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task is novel, there is increased activity in the DLPFC and *reduced* activity in temporal/insula areas. When the task has been practised, there is no longer increased activity in the DLPFC, and the temporal/insula areas show *increased* activity. Poor performance on the Wisconsin test typically consists of *perseveration*. Subjects continue to make the repsonse they have just learned, even though it is no longer appropriate. In other words, they treat the task as if it were practised, when they should treat it as novel. It is possible that this inappropriate strategy is associated with a lack of frontal activation.

Another complex 'frontal' task is the Tower of London test of planning. Andreasen *et al* (1992) have shown that chronic schizophrenic patients perform this task badly and fail to activate the anterior cingulate cortex. This result could also reflect the use of inefficient strategies which do not engage 'frontal' processes. With this task, the problem is not perseveration. Rather, it is the inappropriate attainment of easy short-term goals which are incompatible with the final goal. This reflects the impulsive, rather than perseverative, behaviour characteristic of patients with frontal lesions.

Our results suggest that the method of paced verbal fluency imposed sufficient constraint for all subjects to adopt appropriate strategies. With this task, we have clear evidence that even chronic schizophrenic patients with pronounced negative features can activate the left DLPFC. Indeed, it is possible that they have to activate a greater area of cortex to achieve the same rate of word generation.

Performance of 'frontal' tests, such as the verbal fluency task, engages, not just the frontal cortex, but an extended network of brain areas. In particular, there is a reciprocal relationship between activity in the DLPFC and the temporal cortex (Friston *et al*, 1993). This is evidence of *functional* connectivity between these two areas in man which complements the demonstration of anatomical connectivity in the monkey (Goldman-Rakic, 1986).

Our second major observation was that activation of the DLPFC and other areas in schizophrenic patients was not associated with the relative decrease in blood flow in the left superior temporal gyrus that is observed in normal volunteers. This observation is consistent with a lack of connectivity between these areas. That schizophrenia is a result of frontotemporal disconnection has been suggested previously (e.g. Gold & Weinberger, 1991) on the basis of data from structural and functional brain-imaging studies. In addition, previous attempts to describe the neuropsychological basis of specific signs and symptoms have implicated temporal overactivity, in some accounts explicitly as a consequence of frontotemporal disconnections ( e.g. Frith, 1992, chapter 5).

The superior temporal gyrus is an area of cortex which has a major role in the representation of words. In our first study of brain activity associated with verbal fluency, we suggested (Frith *et al*, 1991*a*) that the reduced activity in this area might reflect the process by which words that have been automatically activated (e.g. *fish – chips*), but are not in the appropriate category (*animals*) are inhibited. On this account, we would expect only disorganised patients to show abnormal activity in the superior temporal cortex, since only these patients produce inappropriate words (Allen *et al*, 1993). However, a more detailed analysis of the kind of neural mechanisms that might underlie intrinsic word generation (Friston *et al*, 1991) suggested that retrieval of words in particular categories (in addition to rejection of inappropriate words) would be more successful when the overall activity in the network in which words were represented was reduced. By this account, we would expect abnormal activity in the superior temporal cortex to be associated with poor verbal fluency of any kind, whether involving failure to produce words or production of inappropriate words. Our detailed experimental investigation of verbal fluency in schizophrenia (Allen *et al*, 1993) also suggested that intrinsic generation processes were impaired in patients with poverty of speech, as well as in those with disorganised speech. Thus, both negative and positive behavioural signs can plausibly be associated with failure of inhibitory processes in brain areas concerned with representation of words. Why, then, did our third group of patients, who had not speech disorders, but hallucinations and delusions, also show this lack of 'inhibition'?

We have proposed that certain types of auditory hallucinations occur when patients perceive their own subvocal, or inner speech as coming from an external agent (Frith, 1992, chapter 5). The normal recognition that our own speech (or action) is indeed our own is a complex process. It depends on mechanisms such as corollary discharge, by which signals are sent from those brain areas involved in initiating the motor components of the action to the brain areas which will receive sensory stimulation as a result of the action. There is evidence that less activity occurs in the temporal cortex in response to the subject's own voice than to the voice of another. It is possible that this reduction of activity is the consequence of inhibitory signals arising from vocalisation areas (e.g. Broca's area, the anterior cingulate cortex) in the frontal cortex. By this account, hallucinations may also be associated with abnormal connectivity between frontal and temporal cortex. Certain delusions (such as delusions of control) can be explained in terms of similar

mechanisms, although different areas of the posterior cortex (concerned with actions other than speech) would be involved. It is also possible that negative features such as poverty of action are associated with frontostriatal disconnections (Robbins, 1990).

We have shown that a number of different, but typical, features of schizophrenia could arise from abnormal connectivity between the frontal and the temporal cortex, leading to disinhibition in the latter area. The results of our functional imaging study provide direct evidence for a lack of inhibition in the temporal cortex in schizophrenic patients, whatever their particular symptoms. We therefore propose that abnormal temporo-frontal connectivity is the key deficit in (chronic) schizophrenia.

Our analysis has not revealed any differences among the three groups of patients. We examined only six circumscribed brain areas, and it may well be that differences are present elsewhere in the brain. This possibility is currently being investigated. However, it is also possible that such differences are best revealed in unconstrained circumstances (i.e. resting scans) when the characteristic mental state of the patient can emerge. Evidence to date suggests that these differences largely concern the direction and location of frontal activations.

We recognise that this is a preliminary result from a small group of patients. It will be necessary to conduct further studies to replicate the result, and to demonstrate that it is not dependent on medication, and that it does not occur in psychiatric patients who do not have psychotic symptoms. If the result is robust, we can say that functional imaging now has the capability to provide direct measures of functional connectivity between brain areas (Friston *et al*, 1993). Such measures are not critically dependent on the activation tasks that are used, so that problems of task performance and compliance become less important. Studies of the precise details of the dysfunctional connectivity within different systems are likely to provide explanations for specific signs and symptoms associated with schizophrenia.

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